AUSTRALIAN PRODUCT INFORMATION

CMV Immunoglobulin-VF

(Human cytomegalovirus immunoglobulin)

1 NAME OF THE MEDICINE

Human Cytomegalovirus Immunoglobulin

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

CMV Immunoglobulin-VF is a sterile, preservative free solution containing 55–65 mg/mL plasma proteins of which at least 98% is immunoglobulins (mainly IgG), with a cytomegalovirus (CMV) immunoglobulin activity of 1.5 million units per vial. The content of CMV immunoglobulin is defined in terms of EIA (enzyme immunoassay) units. One unit is equivalent to the specified volume of a standard CMV Immunoglobulin. Isotonicity is achieved by the addition of 292 mmol/L maltose. The distribution of the IgG subclasses closely resembles that found in normal human plasma (approximate mean ranges: 52.5–64.9% IgG_1, 29.0–42.2% IgG_2, 3.1–6.8% IgG_3, 0.4–1.2% IgG_4). CMV Immunoglobulin-VF contains only trace amounts of IgA (nominally <0.5 mg/mL).

CMV Immunoglobulin-VF is manufactured from human plasma collected by Australian Red Cross Lifeblood.

3 PHARMACEUTICAL FORM

Solution for intravenous injection.

The pH value of the solution is 4.25.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

CMV Immunoglobulin-VF is indicated for the prevention of CMV infection following bone marrow and renal transplants. Specifically, the product is indicated when the recipient is seronegative for CMV and receives a graft from a CMV positive donor.
CMV Immunoglobulin-VF may also be a helpful adjunct to therapy in patients with established CMV infection, e.g. CMV pneumonitis.

4.2 DOSE AND METHOD OF ADMINISTRATION

Dosage

Because there is currently no international standard for CMV Immunoglobulin-VF, recommended dosage remains empirical. For prophylactic use it is recommended that patients receive 25,000 units/kg on days -4, -2, on the day of transplantation (intra-operatively) and then weekly for a further two months.

For therapy, 50,000 units/kg should be given initially, repeated after 4 to 5 days and then every 10 to 14 days until clinical improvement occurs.

Refer to **Table 1** for dosing requirements. If the calculated quantity of CMV Immunoglobulin-VF required for patients weighing >15 kg includes a fraction of a vial, then the higher whole number of vials should be administered.

Specifically, patients weighing ≤15 kg must be dosed based on their body weight (units/kg). Each vial of CMV Immunoglobulin-VF contains at least 20,000 units/mL of CMV immunoglobulin activity. The actual volume is stated on the label. If only a portion of the vial is used, discard the residual volume. Do not administer the whole vial. The volume and acid load should be considered if CMV Immunoglobulin-VF is administered to neonates.

Table 1: CMV Immunoglobulin-VF dosage based on body weight

Body weight (kg)	Dosage in number of vials	
	Prophylaxis	Therapy
0–≤15	<1 vial – Dosage based on body weight (units/kg)	
>15–30	1	1
31–60	1	2
61–90	2	3
91–120	2	4

Administration

If the product appears to be turbid by transmitted light or contains any sediment it must not be used, and the vial should be returned to Australian Red Cross Lifeblood. **The product does not contain an antimicrobial preservative. It must, therefore, be used immediately after opening the vial. Any unused solution must be discarded appropriately. Use in one patient on one occasion only. Do not use if the solution has been frozen.**

CMV Immunoglobulin-VF must be administered intravenously only.
CMV Immunoglobulin-VF may be infused undiluted. Allow the preparation to reach room temperature before infusing into the patient. Remove the dust cover from the top of the vial.

Apply a suitable antiseptic such as povidone-iodine or 70% ethanol to the exposed part of the rubber stopper and allow to dry.

It is usual to gradually increase the infusion rate (provided the patient's vital signs are satisfactory at the lower rate) to the desired rate over the first 30 minutes. The infusion may be commenced at the rate of 1 mL per minute. After 15 minutes the rate may be gradually increased to a maximum of 3 to 4 mL per minute over a further 15 minutes.

Compatibility with other medicines

CMV Immunoglobulin-VF may be diluted with up to four times its volume of 0.9% saline or 5% glucose. No other medicine interactions or compatibilities have been evaluated. CMV Immunoglobulin-VF should be administered separately from other intravenous fluids or medications the patient is receiving.

4.3 CONTRAINDICATIONS

CMV Immunoglobulin-VF is contraindicated in individuals who have had a true anaphylactic reaction to a human immunoglobulin preparation. Individuals with isolated IgA deficiency should not receive the preparation, unless they have been tested and shown not to have circulating anti-IgA antibodies, since these patients may experience severe reactions to the IgA which is present in trace amounts.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

CMV Immunoglobulin-VF MUST be administered intravenously only. Other routes of administration have not been evaluated. It is possible that CMV Immunoglobulin-VF may, on rare occasions, cause a precipitous fall in blood pressure and a clinical picture of anaphylaxis. These reactions may be related to the rate of infusion. Accordingly, the infusion rate given under section 4.2 Dose and method of administration should be closely followed at least until the physician has had sufficient experience with a given patient. The patient's vital signs should be monitored regularly and careful observation made for any symptoms throughout the entire infusion. Adrenaline (epinephrine), oxygen, antihistamine and steroids should be available for the treatment of acute anaphylactic reactions.

An Aseptic Meningitis Syndrome (AMS) has been reported to occur infrequently in association with human intravenous immunoglobulin (IVIG) treatment. The syndrome usually begins within several hours to two days following IVIG treatment. It is characterised by symptoms and signs including severe headache, nuchal rigidity, drowsiness, fever, photophobia, painful eye movements, and nausea and vomiting. Cerebrospinal fluid (CSF) studies are frequently positive with pleocytosis, predominantly from the granulocytic series, and elevated protein levels. Patients exhibiting such symptoms and signs should receive a thorough neurological examination, including CSF studies, to rule out other causes of

meningitis. AMS may occur more frequently in association with high dose (2 g/kg) IVIG treatment. Discontinuation of IVIG treatment has resulted in remission of AMS within several days without sequelae.

There have been occasional reports of renal dysfunction and acute renal failure in patients receiving IVIG products. Patients at increased risk are those with pre-existing renal insufficiency, diabetes mellitus, age greater than 65 years, volume depletion, sepsis and paraproteinaemia, and those taking concomitant nephrotoxic medicines. The majority of such incidents have been associated with sucrose-containing products. Whilst there is no sucrose in CMV Immunoglobulin-VF the following precautions should be followed: patients should be adequately hydrated prior to the initiation of the IVIG infusion and the recommended dose should not be exceeded. Renal function should be monitored in patients at increased risk of developing acute renal failure. If renal function deteriorates, discontinuation of IVIG should be considered.

There is clinical evidence of an association between IVIG administration and thromboembolic events which is assumed to be related to a relative increase in blood viscosity through the high influx of immunoglobulin in at-risk patients. Caution should be exercised when prescribing and infusing IVIG for patients with pre-existing risk factors for thrombotic events such as advanced age, estrogen use, in-dwelling vascular catheters, a history of venous or arterial thrombosis, acquired or inherited hypercoagulable states, cardiovascular risk factors (including history of atherosclerosis and/or impaired cardiac output), prolonged periods of immobilisation, severe hypovolaemia, hyperviscosity (including cryoglobulins, fasting chylomicronemia and/or high triglyceride levels, and monoclonal gammopathies). Reports have included cases of thrombophlebitis. In case of thromboembolic adverse reaction, the benefit and risk of treatment should be assessed before IVIG therapy is continued.

In patients at risk for thromboembolic adverse reactions, IVIG products should be administered at the minimum rate of infusion and dose practicable, and these individuals should be monitored for thrombotic complications. Consideration should also be given to measurement of baseline blood viscosity in individuals at risk for hyperviscosity.

IVIG products can contain blood group antibodies which may act as haemolysins and induce *in vivo* coating of red blood cells with immunoglobulin, causing a positive direct antiglobulin reaction (Coombs' test) and, rarely, haemolysis. Haemolytic anaemia can develop subsequent to IVIG therapy due to enhanced red blood cells (RBC) sequestration. Patients at increased risk for haemolysis following treatment with immunoglobulin include those with non-O blood group types, those who have underlying associated inflammatory conditions, and those receiving high cumulative doses of immunoglobulin over the course of several days. IVIG recipients should be monitored for clinical signs and symptoms of haemolysis, particularly

those patients at increased risk. If these occur, appropriate laboratory testing should be obtained.

In patients with limited or compromised acid-base compensatory mechanisms including neonates, consideration should be given to the effect of the additional acid load that the preparation might present.

Pathogen safety

This product is made from human plasma. Products made from human plasma may contain infectious agents, such as viruses and theoretically Creutzfeldt-Jakob Disease (CJD) agents that can cause disease. The risk that such products will transmit an infectious agent has been reduced by screening plasma donors for prior exposure to certain infectious agents and by testing for the presence of certain viral markers.

In addition, the manufacturing process for CMV Immunoglobulin-VF contains specific steps to reduce the possibility of viral transmission including low pH incubation for viral inactivation and nanofiltration for virus removal. The current procedures applied in the manufacture of this product are effective against enveloped viruses such as human immunodeficiency virus (HIV), hepatitis B virus (HBV), hepatitis C virus (HCV), and the non-enveloped viruses, such as hepatitis A virus (HAV) and human parvovirus B19.

Immunoglobulins for intravenous injection, prepared by this process have not been implicated in the transmission of human immunodeficiency virus (HIV). Studies using plasma spiked with HIV have shown that the Cohn cold-ethanol fractionation process produces a very large reduction in virus titre with undetectable levels in the immunoglobulin fraction. Studies have shown that incubation at 27°C and pH 4.25, as performed in the manufacture of this product, also produces a very large reduction in HIV titre. Epidemiological studies have not recognised any cluster of AIDS patients or HIV seroconversion in immunoglobulin recipients.

Despite these measures, such products may still potentially transmit disease. There is also the possibility that other known or unknown infectious agents may be present in such products.

Vaccination should be considered where appropriate, for patients in receipt of medicinal products manufactured from human plasma.

Use in the elderly

The use of this product in the elderly population has not been established in appropriate studies. To date, this population is not over-represented in spontaneous reports of adverse events associated with the use of CSL’s IVIG therapeutic medicines.

Paediatric use

The use of this product in the paediatric population has not been established in appropriate studies. To date, this population is not over-represented in spontaneous reports of adverse events associated with the use of CSL's IVIG therapeutic medicines.

Effects on laboratory tests

After injection of immunoglobulin, the transitory rise of the various passively transferred antibodies in the patient's blood may result in misleading positive results in serological testing.

Interference with glucose estimations

The maltose present in CMV Immunoglobulin-VF may interfere with some blood glucose measurements, resulting in the overestimation of blood glucose results. If this glucose measurement is used to guide treatment, hypoglycaemia may occur. Only certain glucose tests using glucose dehydrogenase have been implicated, so when monitoring glucose levels in patients receiving CMV Immunoglobulin-VF, information from the manufacturer of the glucose meter and/or test strips, should be reviewed to ensure that maltose does not interfere with the blood glucose reading.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Live attenuated virus vaccines: Passively acquired antibody can interfere with the response to live, attenuated virus vaccines. Therefore, administration of such vaccines, e.g. poliomyelitis or measles, should be deferred until approximately three months after passive immunisation. By the same token, immunoglobulins should not be administered for at least two weeks after a vaccine has been given.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

No reproductive toxicity studies have been conducted with CMV Immunoglobulin-VF. There have been no reports of such effects associated with the use of CSL's plasma-derived therapeutic medicines.

Use in pregnancy

The safety of CMV Immunoglobulin-VF for use in human pregnancy has not been established in controlled clinical trials and therefore it should be given to pregnant women only if clearly needed. However, clinical experience with other immunoglobulin preparations given during pregnancy suggests that there are no adverse effects on the foetus.

Use in lactation

Immunoglobulins are excreted in breast milk and may contribute to the transfer of protective antibodies to the neonate. It is not known, however, whether this applies to passively administered CMV Immunoglobulin-VF. Clinical experience with immunoglobulins suggests that no harmful effects on the neonate are to be expected.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Reactions to IVIG tend to be related to the infusion rate and are most likely to occur during the first hour of the infusion. It is recommended that the patient's vital signs and general status be monitored regularly throughout the infusion.

The types of reactions that may occur include: abdominal pain, headache, chest-tightness, facial flushing or pallor, feeling hot, dyspnoea, non-urticarial skin rash, itching, hypotension, nausea or vomiting. Should any of these reactions develop during infusion of CMV Immunoglobulin-VF, the infusion should be temporarily stopped until the patient improves clinically (5 to 10 minutes) and then cautiously recommenced at a slower rate.

Some patients may develop delayed adverse reactions to CMV Immunoglobulin-VF such as nausea, vomiting, chest pain, rigors or aching legs. These adverse reactions occur after the infusion has stopped but usually within 24 hours.

True anaphylactic reactions to IVIG such as urticaria, angioedema, bronchospasm or hypotension occur very rarely. Should an anaphylactic reaction to CMV Immunoglobulin-VF develop, the infusion should be stopped and treatment instituted with adrenaline (epinephrine), oxygen, antihistamine and steroids.

There have been reports that IVIG can affect renal function. This should be monitored in patients with pre-existing renal failure who are given CMV Immunoglobulin-VF.

Rarely, renal dysfunction and acute renal failure have been reported.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

Overdosage may lead to fluid overload and hyperviscosity, particularly in the elderly and in patients with renal impairment.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Donations are selected on the basis that they contain high levels of specific antibodies to the CMV. The protein has not been chemically or enzymatically modified.

Clinical trials

No data available.

5.2 PHARMACOKINETIC PROPERTIES

The serum half-life of CMV Immunoglobulin-VF is normally approximately three weeks, but may be shortened considerably in patients who are immunosuppressed.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

No genotoxicity studies have been conducted with CMV Immunoglobulin-VF. There have been no reports of such effects associated with the use of CSL's plasma-derived therapeutic medicines.

Carcinogenicity

No carcinogenicity studies have been conducted with CMV Immunoglobulin-VF. There have been no reports of such effects associated with the use of CSL's plasma-derived therapeutic medicines.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Refer to Section 2 Qualitative and quantitative composition.

6.2 INCOMPATIBILITIES

Refer to Section 4.2 Dose and method of administration.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store at 2°C to 8°C (Refrigerate. Do not freeze). Protect from light.

Do not use after the expiry date.

6.5 NATURE AND CONTENTS OF CONTAINER

CMV Immunoglobulin-VF is available in single vials each containing 1.5 million units of CMV immunoglobulin activity.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure

Not applicable

CAS Number

None assigned

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4

8 SPONSOR

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10 DATE OF REVISION

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SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
All	PI updated to the new format.
2, 4.2, 8	Name changed to Australian Red Cross Lifeblood